NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™) GUIDELINE SYNTHESIS

SCREENING FOR PROSTATE CANCER

Guidelines

1. American Urological Association, Inc. (AUA). Prostate specific antigen: Best practice policy. Baltimore (MD): American Urological Association, Inc., 1999. 30 p [130 references].
2. Singapore Ministry of Health (MOH). Prostate cancer. Singapore: Ministry of Health (Singapore); 2000 May. 49 p. (Ministry of Health Singapore clinical practice guidelines; no. 3/00). [168 references]
3. American Cancer Society (ACS). Recommendations from the American Cancer Society Workshop on Early Prostate Cancer Detection, May 4-6, 2000 and ACS guideline on testing for early prostate cancer detection: update 2001. CA Cancer J Clin 2001 Jan-Feb;51(1):39-44 [181 references].
4. U.S. Preventive Services Task Force (USPSTF). Screening for prostate cancer: recommendations and rationale. Ann Intern Med 2002 Dec 3;137(11):915-6 [8 references].

INTRODUCTION:

A direct comparison of AUA, Singapore MOH, ACS, and USPSTF guidelines on screening for prostate cancer is provided in the following tables. The supporting evidence is classified and identified with the major recommendations from the Singapore MOH and USPSTF. The definitions of their rating schemes are included in the last rows of Table 2.

Following the content comparison, areas of agreement and differences among the guidelines are discussed.

Abbreviations:

- ACS, American Cancer Society
- AUA, American Urological Association
- DRE, digital rectal examination
- PSA, prostate specific antigen
- MOH, Ministry of Health
- USPSTF, U.S. Preventive Services Task Force

TABLE 1: COMPARISON OF SCOPE AND CONTENT

AUA (1999)	Objective: To provide current information on the use of PSA testing for 1) early detection of prostate cancer, 2) assistance in pretreatment staging, and 3) the post-treatment monitoring and management of men with this disease. Interventions and Practices Considered: • DRE • PSA • Transrectal ultrasound Target Population: • Asymptomatic men age 50 or over with an anticipated life expectancy of 10 or more years • Asymptomatic men age 40 to 50 years old with a family history of prostate cancer or African-American ethnicity with an anticipated life expectancy of 10 or more years
Singapore MOH (2000)	Objective: To provide recommendations for the management of patients with prostate cancer. Interventions and Practices Considered: • DRE • PSA Interventions for the diagnosis, management and treatment of prostate cancer are also presented in the guideline. Transrectal ultrasound with and without biopsy is discussed in the context of diagnosis rather than screening. Target Population: Asian men, 40 years of age and older with the risk factor of having a first degree relative with prostate cancer at a young age (< 60 years)
ACS (2001)	Objectives: • To update the 1997 American Cancer Society guideline pertaining to prostate cancer screening. • To offer recommendations to health care professionals and the public for informed decision-making related to early detection of prostate cancer

	Interventions and Practices Considered: • DRE • PSA Target Population: • Men aged 50 years and older who have a life expectancy of at least 10 years and younger men who are at high risk for prostate cancer • Men aged 45 years and older of Sub-Saharan African descent or with first-degree relative diagnosed at a young age • Men 40 and older with multiple first-degree relatives diagnosed with prostate cancer at an early age
USPSTF (2002)	Objectives: • To summarize the current USPSTF recommendations on screening for prostate cancer and the supporting scientific evidence • To update the 1996 recommendations contained in the Guide to Clinical Preventive Services, second edition Interventions and Practices Considered: • DRE • PSA Target Population: • Men aged 50-70 years who are at average risk • Men over age 45 who are at increased risk (African American men and men with a family history of a first-degree relative with prostate cancer)

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR PROSTATE CANCER SCREENING

AUA (1999)	Targeted screening Early detection of prostate cancer should be offered to asymptomatic men 50 years of age or older with an estimated life expectancy of more than 10 years. It is reasonable to offer testing at an earlier age to men with defined risk factors, including men with a first-degree relative who has prostate cancer and African

	American men. Informed decision-making Decisions regarding early detection of prostate cancer should be individualized and benefits and consequences should be discussed with the patient before PSA testing occurs. Not all men over age 50 are appropriate candidates for screening efforts for this disease. Ideally, physicians should consider a number of factors including patient age and comorbidity as well as preferences for the relevant potential outcomes. Some organizations have even recommended that informed consent should be obtained prior to PSA testing. Screening tests PSA testing detects more tumors than does DRE, and it detects them earlier. However, the most sensitive method for early detection of prostate cancer uses both DRE and PSA. Both tests should be employed in a program of early prostate cancer detection. Evidence from three uncontrolled studies that allow a direct comparison of the yields of PSA and DRE suggests that combining both tests improves the overall rate of prostate cancer detection when compared with either test alone. The value of serial determinations of PSA or serial DRE in patients with a normal initial examination is unknown. There is evidence that serial PSA determinations lead to a decrease in detection of pathologically advanced disease. Transrectal ultrasonography is not a useful test for early prostate cancer detection; it adds little to the combination of PSA and DRE.
Singapore MOH (2000)	Routine screening At present, population-based screening is not recommended among Asians. (Grade A, Level Ia) Targeted screening All males above 40 years of age with the risk factor of having a first degree relative with prostate cancer at young age (younger than 60 years) may be screened. (Good Practice Point) Screening tests: PSA The appropriate threshold PSA level for the detection of cancer of the prostate is 4.0 ng/mL. (Grade B, Level IIb) Clinically significant cancers are detected by PSA testing. (Grade B, Level IIa)

	PSA-based screening has induced a stage migration but only very preliminary indications of improved survival are available. (Grade C, Level IV) The ratio of free to total PSA levels is recommended as the sensitivity and specificity of levels at 2 to 10 ng/ml for detecting cancer of the prostate is higher. (Grade B, Level IIa) However, the optimal cut-off level is still being investigated. Digital rectal examination Digital rectal examination is recommended as the combination of DRE and PSA test enhances early prostate cancer detection. (Grade B, Level IIa)
ACS (2001)	Targeted screening/Screening tests/Informed decision-making ACS recommends that both the PSA test and the DRE should be offered annually beginning at age 50, to men who have a life expectancy of at least 10 years. Men at high risk should begin testing at age 45. Information should be provided to patients about benefits and limitations of testing. Specifically, prior to testing, men should have an opportunity to learn about the benefits and limitations of testing for early prostate cancer detection and treatment. High-risk groups include men of African descent (specifically, sub-Saharan African descent) and men with a first-degree relative diagnosed at a young age. Risk increases with the number of first-degree relatives affected by prostate cancer.
USPSTF (2002)	Routine screening USPSTF concludes that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or DRE. I recommendation. The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies, and potential complications of treatment of some cancers that may never have affected a patient's health. The USPSTF concludes that evidence is insufficient to determine whether benefits outweigh harms for a screened population. Clinical Considerations • PSA testing and DRE can effectively detect prostate cancer at early pathologic stages. There is insufficient evidence,

	however, that the currently available treatments (radical prostatectomy, radiation therapy, or hormonal therapy) reduce morbidity and mortality from early prostate cancer. Therefore, the benefit of screening for and treating early prostate cancer is unknown. Informed decision-making/Targeted screening/Screening tests/Screening frequency Clinical Considerations • Despite the absence of firm evidence of effectiveness, some clinicians may opt to perform screening for other reasons. Given the uncertainties and controversy surrounding prostate cancer screening, clinicians should not order the PSA test without first discussing with the patient the potential but uncertain benefits (reduction of morbidity and mortality from prostate cancer) and the possible harms (false-positive results, unnecessary biopsies, and possible complications of treatment) of prostate cancer screening. Men should be informed of the gaps in the evidence, and they should be assisted in considering their personal preferences and risk profile before deciding whether to be tested. • If early detection improves health outcomes, the population most likely to benefit from screening will be men aged 50-70 years who are at average risk, and men over age 45 who are at increased risk (African American men and men with a family history of a first-degree relative with prostate cancer). Benefits may be smaller in Asian Americans, Hispanics, and other racial and ethnic groups that have a lower risk of prostate cancer. Older men and men with other significant medical problems who have a life expectancy of fewer than 10 years are unlikely to benefit from screening. • PSA testing is more sensitive than DRE for the detection of prostate cancer. PSA screening with the conventional cut-point of 4.0 ng/dl detects a large majority of prostate cancers; however, a significant percentage of early prostate cancers (10-20%) will be missed by PSA testing alone. Using a lower threshold to define an abnormal PSA detects more cancers at the cost of more false positives and more biopsies. • The yield of screening in terms of cancer detected declines rapidly with repeated annual testing. If screening were to reduce mortality, biennial PSA screening could yield as much benefit as annual screening.
Rating Scheme	
AUA (1999)	Not applicable

Singapore MOH (2000)	Levels of Evidence Level Ia: Evidence obtained from meta-analysis of randomised controlled trials. Level Ib: Evidence obtained from at least one randomised controlled trial. Level IIa: Evidence obtained from at least one well-designed controlled study without randomisation. Level IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study. Level III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies. Level IV: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Grades of Recommendation Grade A (evidence levels Ia, Ib): Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation. Grade B (evidence levels IIa, IIb, III): Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. Grade C (evidence level IV): Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality. Good Practice Points: Recommended best practice based on the clinical experience of the guideline development group.
ACS (2001)	Not applicable
USPSTF (2002)	USPSTF grades its recommendations according to one of five classifications (A, B, C, D, or I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms). A The USPSTF strongly recommends that clinicians routinely provide

	[the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.) B The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves health outcomes and concludes that benefits outweigh harms.) C The USPSTF makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms it too close to justify a general recommendation.) D The USPSTF recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.) I The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.) USPSTF grades the quality of the overall evidence on a 3-point scale (good, fair, or poor). Good Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. Fair Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine

	practice; or indirect nature of evidence on health outcomes. Poor Evidence is insufficient to assess the effects on health outcomes because of limited number of power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

TABLE 3: BENEFITS AND HARMS	
POTENTIAL BENEFITS ASSOCIATED WITH PROSTATE CANCER SCREENING	
AUA (1999)	PSA testing detects more tumors than does DRE and detects them earlier. Although many of these tumors have aggressive characteristics, some may grow slowly enough that they pose no risk to the patient. As yet, there is no way to identify with certainty the tumor that has no risk of spreading and potentially causing premature death or morbidity.
Singapore MOH (2000)	While the incidence of prostate cancer is substantially lower than that in many Western countries, it has been increasing even after having corrected for life expectancy. The majority of patients with prostate cancer present with locally advanced and/or metastatic disease at the time of first diagnosis. The prognosis of advanced prostate cancer is poor despite the most aggressive treatment. Cure is impossible for metastatic prostate cancer. The median time to progression and median survival is approximately 18 and 30 months respectively. Such data contrast sharply with the results of treatment for localized disease where medial survival has been shown to be longer than 15 years. The observed crude survival rates are identical to the expected survival of age-matched controls. As such, it is reasonable to strive for early diagnosis and treatment in the hope of survival benefits. However, uncertainties of the natural history of the disease and efficacy of treatment due to the lack of randomised control studies still cast doubts on the potential benefits of a screening programme. The combination of DRE and PSA enhances early detection. Clinically significant cancers are detected by PSA testing. PSA-based screening has induced a stage migration, but only very preliminary indications of improved survival are available.
ACS (2001)	Prostate cancer screening may result in the diagnosis of earlier-stage disease in younger men, which may decrease prostate

	cancer mortality rates. However, no direct evidence exists to show that prostate-specific antigen (PSA) screening decreases prostate cancer mortality rates.
USPSTF (2002)	Effectiveness of Early Detection USPSTF found one randomized, controlled trial (RCT), and three case-control studies examining the effect of screening on prostate cancer mortality. The single RCT of PSA and DRE screening, which reported a benefit from screening, was hampered by a low rate of acceptance of screening in the intervention group (24%), and by flaws in the published analysis; no difference in prostate cancer deaths was observed between the groups randomized to screening versus usual care using "intention to treat" analysis. Three case-control studies of screening DRE produced mixed results. A number of RCTs of PSA screening for prostate cancer are under way in both the U.S. and Europe, but they are not expected to report results for several years. Data are also limited to determine whether and how much treatment of screen-detected cancers improves outcomes. No properly controlled, prospective studies are available to determine whether prostatectomy or radiation, the most commonly used treatments for prostate cancer, reduce mortality or are more effective than "watchful waiting" for organ-confined prostate cancer. Several such trials are currently under way. In observational studies, outcomes are worst, and the potential impact of aggressive treatment greatest, for poorly differentiated cancers. In the absence of better data on which treatments are effective for which tumors, the USPSTF concluded that it could not determine whether the increased detection of prostate cancer from screening would reduce mortality and morbidity. The USPSTF also examined a variety of ecologic data, including studies of secular trends in prostate cancer mortality after introduction of PSA screening and comparisons of prostate cancer mortality rates in communities with and without screening. Prostate cancer mortality rates in the U.S. have declined since 1991. However, the available ecologic studies have not provided sufficient evidence that prostate cancer trends in the U.S. or other populations are attributable to screening; differences in prostate cancer treatment, underlying risk factors, and how deaths are classified can all introduce bias into ecological comparisons.
POTENTIAL HARMS ASSOCIATED WITH PROSTATE CANCER SCREENING	
AUA (1999)	Tradeoff associated with improving PSA sensitivity: Both age-adjusted PSA and PSA velocity will increase the number of cancers detected, but both will also increase the number of men

	undergoing biopsy. Tradeoff associated with improving PSA specificity: All three methods to improve PSA specificity (age-adjusted PSA, free-to-total PSA ratio, PSA density) will reduce the number of biopsies in men who do not have prostate cancer but will increase the risk that some prostate cancers will be missed. Complications of confirmatory testing: Prostate biopsy by means of a transrectal ultrasound guide, are rarely complicated by rectal bleeding, hematuria, or prostatic infection. After biopsy, blood in the stool or urine usually disappears in a few days. Blood in the semen can be seen for up to several weeks after biopsy.
Singapore MOH (2000)	Not stated
ACS (2001)	Since prostate-specific antigen is prostate-tissue specific and not prostate-cancer specific, there is no absolute value that is applicable to all men. The range of "normal" prostate-specific antigen levels has conventionally been considered to be between zero and 4.0 ng/dl. A lower cut-off value of 2.5 ng/dl has been shown to improve the early detection of organ-confined prostate cancers; however, this also increases the number of men undergoing biopsy in whom no cancer is detected.
USPSTF (2002)	Evidence about the harms of screening per se is scant. The screening process is likely associated with some increase in anxiety, but the number of men affected and the magnitude of the increased anxiety are largely unknown. Some screening procedures cause transient discomfort. Fewer than 10% of men have ongoing interference with daily activities after biopsy, and fewer than 1% suffer more serious complications, including infections. Screening may result in harm if it leads to treatments that carry side effects without improving outcomes from prostate cancer, especially for cancers that have a lower chance of progressing. Erectile dysfunction, urinary incontinence, and bowel dysfunction are well-recognized and relatively common adverse effects of treatment with surgery, radiation or androgen ablation, but men differ in their responses to these symptoms.

GUIDELINE CONTENT COMPARISON

The American Urological Association (AUA), the Singapore Ministry of Health (MOH), the American Cancer Society (ACS), and the U.S. Preventive Services

Task Force (USPSTF) present recommendations for screening men for prostate cancer and provide explicit reasoning behind their judgments.

The guideline from the Singapore MOH provides recommendations for diagnosis, treatment, and management of prostate cancer in addition to the recommendations for screening for the disease. The focus of the AUA guideline is PSA testing, and recommendations are provided for the use of this test in screening, pretreatment staging, and post-treatment management of men with prostate cancer.

The Singapore MOH guideline targets Asian men, whereas the AUA, ACS, and USPSTF guidelines target American men.

Areas of Agreement

Routine screening

All four organizations cite the lack of proof that screening can reduce mortality from prostate cancer. AUA, Singapore MOH, and ACS recommend against routine screening; USPSTF does not recommend for or against routine screening. In addition, AUA, ACS and USPSTF address the clear potential that screening will increase treatment-related morbidity. The Singapore MOH is explicit in their recommendations against routine prostate cancer screening in Asian males.

Targeted screening / Informed decision-making

As the incidence of prostate cancer increases with age, AUA, ACS and USPSTF generally recommend that screening should be offered to men 50 years of age and older with at least a 10-year life expectancy and men less than 50 years of age at risk for developing prostate cancer. These three organizations assert that men should make an informed decision regarding prostate cancer screening with the help of their physicians. Singapore MOH suggests that men be considered for prostate screening if they are above 40 years of age and are at risk for developing prostate cancer.

Screening tests

When the decision to screen is made, there is agreement among the groups that PSA and DRE are the primary screening tests for prostate cancer.

The use of transrectal ultrasound as a screening test for prostate cancer is no longer considered by USPSTF, and the AUA recommends against use of this test. ACS mentions transrectal ultrasound once in their guideline in terms of biopsy. Similarly, the Singapore MOH does not address transrectal ultrasound as a screening test, but rather considers it in combination with biopsy for diagnostic purposes.

Areas of Differences

Screening tests

Although there is agreement among all the groups on the use of PSA and DRE as the primary screening tools for prostate cancer, AUA, Singapore MOH, and ACS explicitly recommend combining the two to improve accuracy. The USPSTF notes that when DRE and PSA are combined more cancers are detected than when PSA

is used alone. USPTSF, however, does not recommend the combination because increased detection would be offset by an increase in false-positive results.

There is variation among the four organizations regarding the best methods to improve PSA sensitivity and specificity. All agree that a PSA threshold level of 4.0 ng/dl will detect many cancers but that as many as 10% to 20% may be missed. AUA discusses methods such as age-adjusted PSA and PSA velocity to improve sensitivity and age adjustment, free-to-total PSA ratios, and PSA density to improve specificity. ACS discusses age-specific reference ranges, PSA density, and free-to-total PSA ratios, suggesting the latter method be used to increase testing accuracy in certain scenarios. Singapore MOH does not recommend age-specific ranges or PSA density, and states PSA velocity is probably not useful. This group does recommend use of free-to-total PSA levels, noting, however, that optimal cut-off is still being investigated, and overall, the value of PSA testing in Asian men is not as clear as it is in Western populations. Finally, USPSTF does not recommend any of these methods because there is insufficient evidence that these variations will improve the accuracy of screening in practice.

Frequency of targeted screening

ACS is the only group that specifically recommends annual screening for men over 50 and younger men at increased risk. In contrast, USPSTF reports that cancer detection declines rapidly with repeated annual testing and suggests biennial screening as equally effective, if screening were to reduce mortality. MOH and AUA do not address the issue of how often screening should be performed.

This Synthesis was prepared by NGC on December 28, 1998 and revised to include additional guideline developers on April 18, 2000. It was reviewed by the guideline developers as of June 27, 2000. Updated recommendations issued by the American Cancer Society (ACS) were incorporated into this synthesis by NGC on April 20, 2001 and were reviewed by the guideline developer as of August 28, 2001. This Synthesis was updated on March 15, 2002 to incorporate Singapore MOH guidelines. Recommendations from USPSTF and CTFPHC were also removed from this Synthesis following their withdrawal from the NGC Web site. This Synthesis was updated again on December 10, 2002 to incorporate updated recommendations issued by the USPSTF. Recommendations from ACPM were removed from this Synthesis on February 02, 2004 following removal of this guideline from the NGC Web site.

Internet citation: National Guideline Clearinghouse (NGC). Guideline synthesis: Screening for prostate cancer. In: National Guideline Clearinghouse (NGC) [website]. Rockville (MD): 1998 Dec 28 (updated 2004 Feb 3). [cited YYYY Mon DD]. Available: http://www.guideline.gov.

© 1998-2004 National Guideline Clearinghouse

Date Modified: 11/1/2004